Pestic. Sci. 1976, 7, 499–502

Insecticidal Activity of the Pyrethrins and Related Compounds

X.[a] 5-Benzyl-3-furylmethyl 2,2-dimethylcyclopropanecarboxylates with ethylenic substituents at position 3 on the cyclopropane ring

Michael Elliott, Andrew W. Farnham, Norman F. Janes,
Paul H. Needham and David A. Pulman

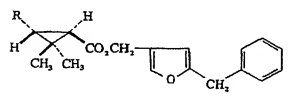
Department of Insecticides and Fungicides, Rothamsted Experimental Station, Harpenden, Herts AL5 2JQ

(*Manuscript received 25 May 1976*)

The insecticidal activities against houseflies (*Musca domestica* L.) and mustard beetles (*Phaedon cochleariae* Fab.) of the chrysanthemate bioresmethrin, and of 31 related 5-benzyl-3-furylmethyl 2,2-dimethylcyclopropanecarboxylates with alkenyl, alkadienyl or alkoxycarbonylalkenyl substituents at position 3 of the cyclopropane ring are compared to determine the relative influence of the isobutenyl sidechain (as in chrysanthemates) and of the other side chains. Several substituents, in particular (*E*)- or (*Z*)-butadienyl or -pentadienyl, give considerably greater activity than isobutenyl but alkoxycarbonyl compounds are less potent.

1. Introduction

This paper complements the preceding one in the series[1] and reports a systematic study of the influence on insecticidal activity of the side chain in the acidic component of esters related to the natural pyrethrins and to bioresmethrin (I; R=—CH=CMe_2). Non-ethylenic replacements for R were considered in the preceding paper;[1] here compounds with one or more centres of unsaturation are examined.



(I)

2. Experimental

2.1. Materials

The syntheses of all of the compounds examined have already been described.[2]

2.2 Methods

Activity against houseflies *Musca domestica* L. and mustard beetles, *Phaedon cochleariae* Fab. was assessed by the methods described previously.[3]

[a] Part IX: *Pestic. Sci.* 1976, 7, 492.

3. Results and discussion

Staudinger and Ruzicka[4] and succeeding workers[5,6] recognised that the nature of the substituent at C-3 on the cyclopropane ring influences the character of the insecticidal activity of pyrethroids; for example, pyrethrin II has faster knockdown but lower killing power than pyrethrin I against most species of insect.[7,8] However, when the present work started, relatively little was known about the effects of modifying this side chain apart from the work of Martel and collaborators.[9,10] Compounds with non-ethylenic substituents at this site were discussed in the preceding paper; here the effects of mono- and di-olefinic groups are considered in one section, and of alkoxycarboxyl compounds related to esters of pyrethric acid in another. This investigation was also stimulated by the observation[11] that an important site for metabolic attack on pyrethroids in mammals is at the *trans*-methyl group of the isobutenyl side chain of chrysanthemates. If the same route [12,13] is important for detoxication in insects, modifying this site by removing the methyl group might increase insecticidal activity; this was tested with some of the compounds described here.

All the esters (see formula I) were of 5-benzyl-3-furylmethanol, and had side chains at C-3 *trans* to the carboxyl function on the cyclopropane ring. Compounds were synthesised as already described,[2] by routes preserving the chiral centre at C-1 in the active (*R*)-configuration; such consistent stereochemistry simplified deductions from the biological results. However, valuable preliminary observations were made with the (±)-*trans*-vinyl and -propenyl compounds.[14]

In the mono-unsaturated series, to both insect species the trend was for insecticidal activity to increase from the vinyl-substituted ester (1; Table 1) to a maximum at the (*Z*)-but-1-enyl compound (4), then diminish with pent-1-enyl and hex-1-enyl esters (5 and 6). Where both geometrical isomers were available (2 and 3), there was little difference in activity to mustard beetles. However, to houseflies (known to have strong mixed function oxidase detoxication systems[15]) the (*Z*)-isomer is more active than the (*E*)-isomer. Of the two forms, the (*Z*)-isomer lacks the appropriately oriented methyl group established as a site for metabolic attack, but detailed investigation would be needed to establish diminished detoxication as the reason for the greater activity. Changing

Table 1. Influence of unsaturation in side chain on relative potency

Compound no.	R in formula (I)[c]	Relative potency to: Houseflies (*Musca domestica* L.)	Relative potency to: Mustard beetles (*Phaedon cochleariae* Fab.)
Bioresmethrin	CH=CMe$_2$ (standard)	1000[a]	1000[b]
1	CH=CH$_2$	680	720
2	CH=CH·Me (*E*)—	650	1300
3	CH=CH·Me (*Z*)—	1500	1100
4	CH=CH·Et (~90% *Z*)—	1600	1600
5	CH=CH·Pr (*Z*)—	640	650
6	CH=CH·Bu (*Z*)—	270	540
7	CH=C(Me)(Et) (50% *E*)—	470	630
8	CH=CH·CH=CH$_2$ (*E*)—	2000	600
9	CH=CH·CH=CH$_2$ (*Z*)—	2000	390
10	CH=CH·CH=CH·Me (*E*)—	1000	780
11	CH=CH·CH=CH·Me (*Z*)—	2000	2000
13	CH=CH·CH=C·Me$_2$ (*E*)—	160	1100
14	CH=CH·CH=C·Me$_2$ (*Z*)—	920	1600
15	CH=C(Me)·CH=CH$_2$ (*Z*)—	1000	1500
16	CH=C(Me)·CH=CH·Me (*Z*)—	740	780

[a] LD_{50} ~6 ng per insect.
[b] LD_{50} ~5 ng per insect.
[c] Configuration given is for C(1)—C(2) bond in R.

either methyl group of the parent isobutenyl compound to ethyl (mixed isomers, 7) diminished activity. Such variations of potency with chain length, unsaturation and branching are probably related to requirements for optimum fit and polarity, as discussed previously.[15,16]

Compounds (8–16) with conjugated dienic unsaturation were generally more active than the mono-olefinic compounds against both species, 4- and 5-carbon substituents being most potent. The degree of unsaturation at this site in the molecule influences local and overall physical properties, and the greater activity of the dienic compounds may be related to the relatively greater potency of pyrethrin I (diene side chain) compared with allethrin (alkene side chain) to most species.[17] Neither the geometrical configuration nor, in the examples here, the position of the methyl substituents was especially important for insecticidal activity. The locations in the molecule of the various groups considered, like oximinomethyl in the preceding paper,[1] are determined by the geometry of the cyclopropane ring. Although the present examples are all *trans*-compounds, the potency of both *cis*- and *trans*-isobutenyl and -dihalovinyl substituted (1*R*)-cyclopropanecarboxylates[6,18,19] indicates that appropriate functions confer activity from either position at C-3.

Okada *et al.*[20] prepared optically active *cis*- and *trans*-2,2-dimethyl-3-vinylcyclopropanecarboxylic acids, but assayed only their allethrolone esters, so that only limited comparison with the present results is possible. Matsui *et al.*[21] made a variety of esters of 2,2-dimethyl-3-vinyl- and 2,2-dimethyl-3-(1-propenyl)cyclopropanecarboxylates of unspecified stereochemistry, with results consequently difficult to interpret. After this work was completed, a patent[22] became available, describing, again without details of stereochemistry, various esters with side chains as in (8–16) as well as 3-methyl- and 2,3-dimethylbutadienyl, 3-methyl-, 4-methyl-, 2,3- and 3,4-dimethyl-, and 2,3,4-trimethylpentadienyl compounds. The biological data agree well with results here; the most active side chains are butadienyl, pentadienyl, and 4-methylpentadienyl, and with a range of 11 alcohols, the (*Z*)-butadienyl compound is 1.5–3.0 times as active as the isobutenyl standard.

It is known, from the structure of pyrethrin II, that esters of pyrethric acid (which has an unsaturated methyl ester function in the side chain at C-3) have significant insecticidal activity, but the relationship between activity and the structures of various other esters of related acids had not been studied. Table 2 shows results with 15 5-benzyl-3-furylmethyl esters of pyrethric and closely related

Table 2. Influence of substitution in unsaturated ester derivatives on relative potency

Compound no.	R in formula I	Relative potency to: Housefies (*Musca domestica* L.)	Relative potency to: Mustard beetles (*Phaedon cochleariae* Fab.)
Bioresmethrin		1000	1000
17	CH=CH·CO_2Me (*E*)—	91	73
18	CH=CH·CO_2Et (*E*)—	67	510
19	CH=CH·CO_2Pr (*E*)—	25	40
20	CH=C(Me)·CO_2Me (*E*)[a]	290	440
21	CH=C(Me)·CO_2Et (*E*)—	280	450
22	CH=C(Me)·CO_2Pr (*E*)—	26	240
23	CH=C(Et)·CO_2Me (*E*)—	130	360
24	CH=C(Et)·CO_2Et (*E*)—	300	290
25	CH=C(Et)·CO_2Pr (*E*)—	23	55
26	CH=C(Cl)·CO_2Me (70:30)[b]	82	340
27	CH=C(Cl)·CO_2Et (70:30)	150	340
28	CH=C(Cl)·CO_2Pr (80:20)	23	120
29	CH=C(Br)·CO_2Et (80:20)	440	320
30	CH=C(CN)·CO_2Et (1 isomer)	140	—
31	CH=C(CN)$_2$	14	non-toxic

[a] NRDC 106 (pyresmethrin).
[b] (*Z*)— and (*E*)— isomers, present in the stated ratio, of compounds 26–30 were not characterised separately.

acids against the two insect species. Compounds (17–19) unsubstituted on C-2 were less active than those (20–25) with methyl or ethyl groups, and ethyl and methyl esters (17, 18, 20, 21, 23, 24) were more active than propyl (19, 22, 25). In this series, unlike the alkenyl, chloro (compounds 26–28) was a less effective substituent than methyl, but the one bromo compound (29) had high activity, especially against houseflies.

All this second series of compounds (Table 2) are less active than the parent bioresmethrin and only slightly more so than the ester (20) of pyrethric acid, the constituent of the natural ester pyrethrin II.

Dihalovinyl,[18,19] butadienyl and pentadienyl side chains are therefore established as substituents on the cyclopropane ring which give useful increases in insecticidal activity over the isobutenyl side chain present in chrysanthemic acid. However, greater stability and ease of synthesis make dihalovinyl esters[24–26] more promising compounds for practical applications.

Acknowledgements

The authors are grateful to Dr G. Pattenden for supplying samples of methyl (±)-*trans*-2,2-dimethyl-3-vinylcyclopropanecarboxylate and methyl (±)-*trans*-2,2-dimethyl-3-(1-propenyl)cyclopropanecarboxylate (*cf* reference 14).

References

1. Elliott, M.; Farnham, A. W.; Janes, N. F.; Needham, P. H.; Pulman, D. A. *Pestic. Sci.* 1976, 7, 492.
2. Elliott, M.; Janes, N. F.; Pulman, D. A. *J. chem. Soc. Perkin I* 1974, p. 2470.
3. Elliott, M.; Farnham, A. W.; Ford, M. G.; Janes, N. F.; Needham, P. H. *Pestic. Sci.* 1972, 3, 25.
4. Staudinger, H.; Ruzicka, L. *Helv. chim. Acta.* 1924, 7, 201.
5. Matsui, M.; Kitahara, T. *Agric. Biol. Chem. Tokyo* 1967, 31, 1143.
6. Barlow, F.; Elliott. M.; Farnham, A. W.; Hadaway, A. B.; Janes, N. F.; Needham, P. H.; Wickham, J. C. *Pestic. Sci.* 1971, 2, 115.
7. Sawicki, R. M.; Elliott, M.; Gower, J. C.; Snarey, M.; Thain, E. M. *J. Sci. Fd Agric.* 1962, 13, 172.
8. Elliott, M.; Needham, P. H.; Potter, C. *J. Sci. Fd Agric.* 1969, 20, 561.
9. Velluz, L.; Martel, J.; Nominé, G. *C.r. hebd. Séanc. Acad. Sci., Paris, Ser. C* 1969, 268, 2199.
10. Lhoste, J.; Rauch, F. *C. r hebd. Séanc. Acad. Sci., Paris Ser. C* 1969, 268, 3218.
11. Elliott, M.; Janes, N. F.; Kimmel, E. C.; Casida, J. E. *J. agric. Fd Chem.* 1972, 20, 300.
12. Yamamoto, I.; Casida, J. E. *J. econ. Ent.* 1966, 59, 1542.
13. Yamamoto, I.; Kimmel, E. C.; Casida, J. E. *J. agric. Fd Chem.* 1969, 17, 1227.
14. Crombie, L.; Doherty, C. F.; Pattenden, G. *J. chem. Soc. (C)*, 1970, p. 1076.
15. Briggs, G. G.; Elliott, M.; Farnham, A. W.; Janes, N. F. *Pestic. Sci.* 1974, 5, 643.
16. Briggs, G. G.; Elliott, M.; Farnham, A. W.; Janes, N. F.; Needham, P. H.; Pulman, D. A.; Young, S. R. *Pestic. Sci.* 1976, 7, 236.
17. Elliott, M.; Needham, P. H.; Potter, C. *Ann. appl. Biol.* 1950, 37, 490.
18. Burt, P. E.; Elliott, M.; Farnham, A. W.; Janes, N. F.; Needham, P. H.; Pulman, D. A. *Pestic. Sci.* 1974, 5, 791.
19. Elliott, M.; Farnham, A. W.; Janes, N. F.; Needham, P. H.; Pulman, D. A. *Pestic. Sci.* 1975, 6, 537.
20. Okada, K.; Fujimoto, K.; Matsui, M. *Agric. Biol. Chem., Tokyo* 1974, 38, 827.
21. Sumitomo Chemical Co. Ltd Ger. Offen. 2 113 124.
22. Sumitomo Chemical Co. Ltd Ger. Offen. 2 231 436.
23. Elliott, M.; Farnham, A. W.; Janes, N. F.; Needham, P. H.; Pulman, D. A. *Nature, Lond.* 1973, 244, 456.
24. Elliott, M.; Farnham, A. W.; Janes, N. F.; Needham, P. H.; Pulman, D. A.; Stevenson, J. H. *Nature, Lond.* 1973, 246, 169.
25. Elliott, M.; Farnham, A. W.; Janes, N. F.; Needham, P. H.; Pulman, D. A.; Stevenson, J. H. *Proc. 7th Br. Insectic. Fungic. Conf.* 1973, 2, 721.
26. Elliott, M.; Farnham, A. W.; Janes, N. F.; Needham, P. H.; Pulman, D. A. *Nature, Lond.* 1974, 248, 710.